REMARKS

Claims 14-22 are currently being examined. Applicants have amended claim 16 to more particularly and distinctly claim that which Applicants regard as their invention. No new matter has been introduced by this amendment.

Applicants request Rejoinder of claims 20-22. Under MPEP § 821.04, if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn method claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined. Applicants assert that claims 14-16 and 18-19 are allowable and because the subject matter of claims 20-22 are of the same scope as the allowable claims in compliance with §821.04, these claims should be rejoined and allowed.

I. Restriction Requirement

The Applicants thank the Examiner for reassessing the restriction requirement and examining Groups I and II together. However, Applicants still contend that there is no additional burden to examine claim 17. The Office contends it would require an additional sequence search. However, the additional interferon molecule comprises the same sequences searched for Group I-II. Therefore, Applicants request that the Examiner withdraw the Restriction related to claim 17 and rejoin Groups III and IV.

II. Claim Objection

Claim 19 has been objected to because it depends from a non-elected claim. Applicants request that this objection be held in abeyance pending a final determination of the Restriction requirement.

III. Information Disclosure Statement

The Office has crossed several references off the IDS submitted upon filing of this divisional application citing 37 CFR 1.98(a)(2). Applicants refer the Examiner to the parent application (09/268,787) in which the references were submitted and reviewed by the previous Examiner. Therefore, according to 37 C.F.R. 1.98(d), Applicants need not resubmit the references submitted in the prior application to obtain consideration of the IDS. Applicants request that the Examiner consider the references crossed off the previous IDS. A new copy of the IDS is provided for the Examiner's convenience.

IV. Priority

Applicants submit that the claims should have priority to at least the parent application (09/268,787) filed March 16, 1999. The current application is a divisional of this parent application and is so referenced in the amended version of the first paragraph, submitted in the preliminary amendment filed on March 20, 2002. Therefore, the priority should be at least March 16, 1999, not October.

V. Double Patenting

In an effort to respond to the Office's rejection, Applicants assume that the Office meant to cite U.S. Patent No. 5,723,125, and not U.S. Patent No. 5,727,125. U.S. Pat. No. 5,727,125 is not owned by Applicants and has nothing to do with Interferon. Applicants request that the requirement to file a Terminal Disclaimer be held in abeyance until allowable subject matter is determined.

VI. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 16 has been rejected as indefinite due to the recitation of the term ADCC. Applicants have amended claim 16 to spell out the acronym, and request that the rejection be withdrawn.

VII. Rejection Under 35 U.S.C. § 112, First Paragraph

A. Written Description

Claims 14-16 and 18-19 have been rejected as failing to comply with the written description requirement. The Office contends that the specification fails to provide adequate written description of the functional IFN-Fc variants because "the skilled artisan cannot envision the detailed underlying mode of making innumerable variants of the IFN-Fc hybrid." (Office Action at page 7). Applicants respectfully traverse this rejection.

Applicants refer to the same Guidelines referenced by the Examiner, specifically Example 14. In that example the conclusion was that variants were supported by the specification even though only a single species was disclosed because the functional language required functional activity of the variant and the specification provided an assay for function. The same is true here. Claim 14 requires that the variant be functional, and the specification provides an assay to test functionality, i.e. Example II

(4). Therefore, Applicants submit that the Guidelines support a determination that the specification provides sufficient written description for the Genus of functional variants claimed and request that the rejection be withdrawn.

B. Enablement

Claims 14-16 and 18-19 have been rejected as lacking enablement. The Office contends that the state of the art is unpredictable and the Applicants have not provided sufficient guidance to produce the functional variants claimed. Applicants respectfully traverse this rejection.

As discussed in section A above, Applicants have claimed "functional variants" and have provided an assay to test such variants in Example II (4). The Office has already stated in the written description guidelines, Example 14, that the procedure for making protein variants such as substitutions, deletions, insertions etc. is conventional and routine, and NOT unpredictable as the Office presently contends. Applicants also assert that the viral assay provided is sufficient guidance to test such variants for functional activity. This testing is not undue, as the specification provides the necessary guidance to perform the assay, the techniques are routine for those skilled in the art, the level of skill in the art is high, there are working examples in the specification, and the prior art discloses numerous sequences associated with interferons. (See for example IDS reference "The Interferon Genes" by Weissmann and Weber, copy provided for Examiner's convenience). In view of all of these factors, Applicants submit that the specification provides an enabling disclosure for the entire breadth of the claimed functional variants, and request that the rejection be withdrawn.

VIII. Rejection Under 35 U.S.C. § 103

Claims 14-16 and 18-19 have been rejected as unpatentable over Landolphi (U.S. Pat. No. 5,349,053), in view of Frincke (EP 467,416) and Peterhans Analytical Biochem). The Office contends that "it would have been prima facie obvious to one of ordinary skill in the art to substitute the interferon/Fc gamma chain fragment molecule of Landolphi with interferon alpha of Frincke to make a hybrid molecule that would be stable for in vivo use because of the recognized stability of hybrid as a preferred use as

set forth by Francke (sic)." (Office Action at page 12-13). Applicants respectfully traverse this rejection.

The Office has failed to meet its burden for establishing its *prima facie* case of obviousness on two grounds. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. See *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). In the present case, there is no suggestion or incentive to combine the references cited by the Office, and there is no reasonable expectation of success.

The Federal Circuit has repeatedly warned that the requisite motivation must come from the prior art, not applicant's specification. See *In re Dow Chem. Co. v. American Cyanamid Co.*, 837 F.2d at 473, 5 U.S.P.Q.2d at 1531-1532 ("[t]here must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure"). Using an applicant's disclosure as a blueprint to reconstruct the claimed invention from isolated pieces of the prior art contravenes the statutory mandate of § 103 of judging obviousness at the point in time when the invention was made. See *Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907, 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988). Moreover, where the prior art has not recognized the "result-effective" capability of a particular invention parameter, no expectation would exist that optimizing the parameter would successfully yield the desired improvement.

Here, the Office has pieced together disparate references using the Applicants' specification as a guide. Landolphi discloses chimeric molecules that "exhibit the high degree of specificity associated with the ligand, yet retain various effector functions characteristic of immunoglobulin heavy chains." (Abstract) These effector functions include fixing complement and/or mediating antibody dependent complement fixation.

(Col. 2, lines 50-53.) The problem being solved was "the need for increasing the specificity and improving binding affinity of immunoglobulins beyond the immunoglobulin gene superfamily, while retaining their useful characterisitics." (Col. 2, lines 30-33.) The IL-2 construct and experiments disclosed further that end. Thus, one would not look to EP467416, because this patent was directed to increasing serum half-life through the use of an antigen antibody complex (not fusion proteins). The method taught by the '416 patent was to bind the antibody to the agent in an antigen-antibody complex, thus attaching the antibody to the agent through its **Variable** region. There is no suggestion that using the construct of Landolfi would accomplish the same thing as the Ag-Ab complex taught by the '416 patent because they are two different approaches. Peterhans goes even further afield because he was making β-galactosidase fusions for ELISA assays, which have nothing to do with *in vivo* half-life. In view of the lack of suggestion or motivation to combine these references, absent the Applicants' specification, the Office has failed to establish a *prima facie* case of obviousness.

The Office has also failed to establish a reasonable expectation of success. In moving from the prior art to the claimed invention, one cannot base a determination of obviousness on what the skilled person might try or find obvious *to try*. Rather, the proper test requires determining what the prior art would have led the skilled person *to do*.

Before a reference can constitute legally cognizable prior art, it must teach how to make what it discloses. *In re Hoeksema*, 399 F.2d 269, 274, 158 U.S.P.Q. 596, 600-01 (C.C.P.A. 1968) held that the "true test of any prior art relied on to show or suggest that a chemical compound is old, is whether the prior art is such as to place the disclosed 'compound' in the *possession of the public*" (emphasis added). The test whether a particular compound described in the prior art may be relied upon to show obviousness is whether the prior art provided an enabling disclosure with respect to the disclosed compound. *Ashland Oil, Inc. v. Delta Resins Refractones* 776 F2d. 281, 227 USPQ 657 (Fed. Cir. 1985). Because the evidence in *Ashland* showed that a certain compound was a "hypothetical structure", the court found it was not persuasive of obviousness.

In this case, the Landolphi patent merely lists lymphokines as possible ligands, with no specific reference to interferons, thus these are merely hypothetical structures with no enabling disclosure. As further evidence of the fact that the Landolphi patent does not enable embodiments other that IL-2, the Examiner stated at page 5 of the Office Action dated March 23, 1992, of the prosecution history of that patent (See Exhibit 1):

> [P]age 7 merely list[s] several lymphokines and growth factors that can be used as the ligand. . . . . [T]he specification is non-enabling for the preparation of immunoligands broadly, nor is it evident that the scope of these immunoligand[s] would have a utility and possess the desired physical and functional properties for each portion of the immunoligand. Lymphokine (LK) is generic, and represent[s] a broad and diverse group of proteins that are functionally and patentably distinct, such that the preparation of an immunoligand with one LK such as IL-2 cannot effectively predict or enable the preparation and usefulness of the entire scope of LK.

Applicants of the Landolphi patent were unable to rebut this rejection and ultimately had to narrow their claims to the immunoligand IL-2. (See Exhibits 2-5). Thus, the Landolphi patent fails to provide the necessary teachings to put the public in possession of the full scope of the invention as disclosed and as such cannot constitute legally cognizable prior art for the presently claimed invention. Moreover, as pointed out by the Examiner of the Landolphi patent, there is no evidence that creating a hybrid molecule comprising an interferon-α molecule joined to an Fc fragment via a linker would "possess the desired physical and functional properties." There is no reasonable expectation of success in making the presently claimed invention in view of the nonenabling disclosure of the Landolphi patent.

The EP467416 fails to overcome the deficiencies in the Landolphi patent. This specification discloses antibody compositions made by creating an antibody ("Ab") directed against the therapeutic agent, e.g., alpha-interferon, such that when the Ab binds to the therapeutic agent, it forms an antibody-interferon complex that does not impair the activity of the agent. However, this does not teach constructing a hybrid molecule wherein the alpha-interferon is joined to the immunoglobulin Fc fragment.

Indeed, not only is the composition taught by EP467416 not a hybrid molecule, the Ab composition disclosed binds to the alpha-interferon through its **variable** region, not the constant region.

Peterhans also does not solve the deficiencies of the Landolphi patent. It merely discloses making β-galactosidase fusions for ELISA assays. This is clearly not a immunoglobulin Fc fragment hybrid molecule and thus, it does not suggest a hybrid interferon-Ig molecule nor does it provide a reasonable expectation of success.

Thus, the Office has not met its burden of establishing a *prima facie* case of obviousness for this additional reason. There is no reasonable expectation of success given the nonenabling teachings of the cited prior art.

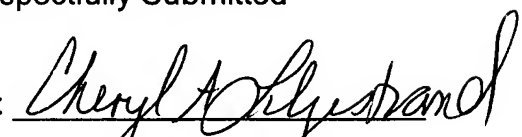
Finally, as further evidence of nonobviousness, evidence is presented at page 6 (last paragraph) of the specification illustrating unexpected results. The *in vivo* pharmokinetic studies in primates resulted in a 40-fold longer serum half-life than unmodified interferon. The clearance half-life after subcutaneous injection was almost 120 fold longer. EP467416 only reported a 12-fold increase in half-life (col. 6, lines 53-57.) Since, the Landolphi patent only constructed IL-2-Ig complexes, and does not disclose any increases in half-life, the present invention clearly demonstrates unexpected results over this patent as well. Peterhans discloses labeled constructs labeled complexes for an entirely different purpose, thus no disclosure of increased half-life.

In view of the lack of a motivation to combine references, a lack of a reasonable expectation of success, and the unexpected results presented in the present disclosure, the § 103(a) rejection should be withdrawn.

Conclusion

In view of the previous remarks, Applicants submit that the claims are in condition for allowance and request rejoinder of claims 17, 20-22.

Respectfully Submitted

By: 

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